EFFECT OF PLASMA POTASSIUM ON VASCULAR RESPONSE TO PRESSOR AND DEPRESSOR AGENTS IN DOG KIDNEY

Keichi Ito, M.D., Satoshi Akabane, M.S.*, and Yohkazu Matsushima, Ph.D.*

The effect of plasma potassium concentration on the vascular response to the pressor agent angiotensin II (ANG II) and to the depressor agent prostaglandin E2 (PGE2) was investigated in dog kidney. Renal vascular reactivity to the vasoactive agents was assessed from the change in renal blood flow (RBF) after infusion of the agent into the renal artery. Plasma potassium concentration was increased by intravenous infusion of potassium L-aspartate solution.

The vascular response to ANG II was attenuated when plasma potassium was increased, i.e., percent decrease in RBF produced by ANG II (26.1 ± 8.4%) during potassium infusion (plasma K+, 5.68 ± 0.31 mEq/L) was significantly lower than those (35.8 ± 9.8, 30.4 ± 7.8%) obtained in the control period (plasma K+, 3.60 ± 0.40 mEq/L) and in the postinfusion period (plasma K+, 4.70 ± 0.42 mEq/L). On the other hand, the vascular response to PGE2 showed a tendency to be potentiated by elevation of plasma potassium concentration, i.e., percent increases in RBF produced by PGE2 were 44.9 ± 10.5% in the control period (plasma K+, 3.47 ± 0.25 mEq/L), 50.5 ± 6.8% during potassium infusion (plasma K+, 5.45 ± 0.25 mEq/L) and 44.9 ± 7.2% in the recovery period (plasma K+, 4.55 ± 0.21 mEq/L). These changes in the vascular response obtained by elevation of plasma potassium appear to act towards lowering blood pressure.

Potassium is known to relate to blood pressure control. For example, a high potassium diet suppresses elevation of blood pressure produced by salt loading in experimental animals. A high potassium intake also lowers the blood pressure of hypertensive patients and hypertensive animals. Many mechanisms have been proposed for the antihypertensive effect of high potassium intake. Change in vascular responses to vasoactive substances has been considered to be one of these mechanisms and there are numerous reports that a high potassium intake may alter the vascular reactivity and pressor response to angiotensin II or norepinephrine. However, the results are conflicting. The pressor response to angiotensin II has been reported to decrease on the one hand and to increase on the other hand by high K+ intake. High K+ intake was found by Hollenberg to enhance the renal vascular reactivity to angiotensin II. On the other hand, Frohlich et al reported that KCl infusion depressed the renal vascular sensitivity to norepinephrine. In addition, most of these studies changed the potassium balance by diet. This method may not be appropriate in studying the effect of changes in

Key Words:
- Plasma potassium
- Vascular response
- Angiotensin II
- Prostaglandin E2

(Received May 21, 1985; accepted December 12, 1985)
Department of Internal Medicine, *Research Institute, National Cardiovascular Center, Osaka, Japan
This work was supported by a Research Grant for Cardiovascular Diseases (56c-2) from the Ministry of Health and Welfare.
Mailing address: Keichi Ito, M.D., Department of Internal Medicine, National Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita, Osaka 565, Japan

Japanese Circulation Journal Vol. 50, March 1986 265
TABLE I  EXPERIMENTAL DATA BEFORE, DURING AND AFTER POTASSIUM INFUSION (EXPERIMENT I)

<table>
<thead>
<tr>
<th></th>
<th>Control period</th>
<th>Potassium period</th>
<th>Recovery period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma K⁺ (mEq/L)</td>
<td>3.60 ± 0.14</td>
<td>5.68 ± 0.31*</td>
<td>4.70 ± 0.42</td>
</tr>
<tr>
<td>Plasma Na⁺ (mEq/L)</td>
<td>153.9 ± 1.1</td>
<td>153.2 ± 1.4</td>
<td>153.6 ± 1.9</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>159 ± 9</td>
<td>162 ± 7</td>
<td>150 ± 12</td>
</tr>
<tr>
<td>Renal blood flow (ml/kg/min)</td>
<td>11.0 ± 2.7</td>
<td>13.6 ± 3.8</td>
<td>13.4 ± 3.9</td>
</tr>
<tr>
<td>Urine flow (ml/min)</td>
<td>0.16 ± 0.02</td>
<td>0.52 ± 0.03**</td>
<td>0.25 ± 0.06</td>
</tr>
<tr>
<td>Sodium excretion (μEq/min)</td>
<td>7.2 ± 2.7</td>
<td>25.2 ± 6.3***</td>
<td>8.9 ± 3.1</td>
</tr>
</tbody>
</table>

* p < 0.01 compared with control and recovery  
** p < 0.001 compared with control and p < 0.05 compared with recovery  
*** p < 0.05 compared with control and recovery

plasma K⁺ concentration. There are also epidemiological reports which showed a negative correlation between blood pressure and plasma K⁺ level\textsuperscript{11,12} However, investigations observing the effect of increases in plasma K⁺ concentration itself are relatively few, and we have not found any reports which studied the effect of plasma K⁺ concentration on the vascular response to depressor substances like prostaglandin or kallikrein. Therefore, we undertook this study to investigate the effect of the increase in plasma K⁺ concentration by acute potassium infusion on the vascular response to the pressor substance angiotensin II (ANG II) and the depressor substance prostaglandin E₂ (PGE₂). We chose the renal vessel for determination of vascular reactivity because the kidneys respond with marked reactivity to plasma potassium level\textsuperscript{13} and are reliable when examining vascular reactivity.

METHODS

Mongrel dogs were anesthetized with 30 mg/kg i.v. sodium pentobarbital and maintained with periodic additional doses. An endotracheal tube was inserted and connected to a respirator (Harvard, model 607). The left renal artery was exposed through a retroperitoneal incision and denervated by stripping the renal nerve and applying 95% ethylalcohol to the renal pedicle. Adequacy of this technique for denervation has been verified\textsuperscript{14,15} Renal blood flow (RBF) was estimated with a noncannulating flow probe positioned around the renal artery and an electromagnetic flow meter (NARCO, RT-500). For infusion of angiotensin II or prostaglandin E₂, the left renal artery was punctured at the site proximal to the flow probe with a fish-hook-shaped 23 gauge needle connected to a polyethylene tube (PE-50). The left ureter was cannulated for collection of urine. Another catheter was placed in the femoral artery and arterial pressure was measured with a pressure transducer (Statham, P23 Db) connected to the catheter. Infusion of 5% glucose solution and potassium was done through a catheter inserted in the cephalic vein. Renal vascular reactivity to ANG II and PGE₂ was investigated by comparison of percent changes in RBF produced by ANG II or PGE₂ injection when plasma K⁺ concentration was changed. The following two experiments were done separately.

Experiment I:

Four dogs weighing from 10 to 13 kg and one dog weighing 32 kg were used in this experiment. Five % glucose solution was infused at a rate of 0.12 ml/kg/min intravenously to keep a constant urine flow for 40 min (control period). Following the control period, 2 mEq/kg/hr of potassium (potassium L-aspartate) was added to the 5% glucose infusion for 40 min (potassium period). Infusion rate of solution during the potassium period, consequently, was the same as that of the control period. After the potassium period, potassium was stopped and 5% glucose solution only was again infused for 40 min (recovery period). To determine the renal vascular response to ANG II, ANG II (Hypertensin, Ciba) was infused through a needle punctured at the renal artery at a rate of 3 ng/kg/min at the end of each period. This infusion was continued until maximal decrease in RBF by this dose of ANG II infusion was obtained, after which ANG II infusion was immediately stopped. The time of infusion of ANG II was approximately 2 min. Blood samplings were done just before each ANG II infusion. Urine was collected for

Japanese Circulation Journal  Vol. 50, March 1986
TABLE II EXPERIMENTAL DATA BEFORE, DURING AND AFTER POTASSIUM INFUSION (EXPERIMENT II)

<table>
<thead>
<tr>
<th></th>
<th>Control period</th>
<th>Potassium period</th>
<th>Recovery period</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma K</strong> (mEq/L)</td>
<td>3.47 ± 0.25</td>
<td>5.45 ± 0.25*</td>
<td>4.55 ± 0.29</td>
</tr>
<tr>
<td><strong>Plasma Na</strong> (mEq/L)</td>
<td>153.4 ± 1.1</td>
<td>152.0 ± 1.1</td>
<td>151.4 ± 0.7</td>
</tr>
<tr>
<td><strong>Mean blood pressure</strong> (mmHg)</td>
<td>125 ± 11</td>
<td>132 ± 9</td>
<td>130 ± 10</td>
</tr>
<tr>
<td><strong>Renal blood flow</strong> (ml/kg/min)</td>
<td>6.7 ± 1.1</td>
<td>7.7 ± 2.0</td>
<td>7.4 ± 1.7</td>
</tr>
<tr>
<td><strong>Urine flow</strong> (ml/min)</td>
<td>0.16 ± 0.01</td>
<td>0.56 ± 0.10**</td>
<td>0.38 ± 0.07</td>
</tr>
<tr>
<td><strong>Sodium excretion</strong> (µEq/min)</td>
<td>15.9 ± 5.7</td>
<td>36.1 ± 4.7**</td>
<td>19.2 ± 4.9</td>
</tr>
</tbody>
</table>

* p < 0.01 compared with control
** p < 0.05 compared with control and recovery

**Experiment II:**

In four dogs weighing from 15 to 25 kg and one dog weighing 12 kg, renal vascular response to PGE₂ was determined in control, potassium and recovery periods. 0.5 mg of PGE₂ was dissolved in 0.25 ml of saline and injected by bolus into the renal artery and the maximal increase in RBF was estimated as renal vascular reactivity to PGE₂. This experiment then followed the same procedures as those in experiment I. All data were expressed as mean ± SEM. Differences between the groups were analyzed by paired Student’s t test.

**RESULTS**

**Experiment I:**

As shown in Table I, plasma concentration of potassium was increased from 3.60 ± 0.40 mEq/L in the control period to 5.68 ± 0.31 mEq/L in the potassium period by potassium infusion and it was again reduced to 4.70 ± 0.42 mEq/L in the recovery period after cessation of potassium infusion. On the other hand, plasma sodium concentration, as seen in Table I, did not change during potassium infusion and was constant through three periods. Mean arterial blood pressure (MAP) was not significantly changed by potassium infusion. RBF showed a tendency to increase, from 11.0 ± 2.7 ml/kg/min in the control period to 13.6 ± 8.4 ml/kg/min in the potassium period by potassium infusion, but the difference was not significant. Although plasma renin activity (PRA) and plasma aldosterone concentration (PAC) were determined in only three dogs, PRA tended to be decreased by potassium infusion (14.4 ± 3.1 ng/ml/hr in the control period, 11.3 ± 4.5 ng/ml/hr in the potassium period, 13.8 ± 3.2 ng/ml/hr in the recovery period.

Fig.1. Changes in renal blood flow (RBF) induced by angiotensin II (A) or prostaglandin E₂ (B) injection.

A: Renal vascular response to angiotensin II was attenuated by elevation of plasma K⁺ concentration during K⁺ infusion compared with those in the control and recovery periods.

B: Renal vascular response to prostaglandin E₂ showed a tendency to be potentiated by elevation of plasma K⁺ concentration, though not significantly.

10 min in each period. Sodium and potassium of plasma and urine were determined by spectrophotometry.

*Japanese Circulation Journal Vol. 50, March 1986*
and PAC tended to be increased by potassium infusion (29.7 ± 9.0 ng/dl in the control period, 35.7 ± 7.9 ng/dl in the potassium period, 30.6 ± 8.3 ng/dl in the recovery period). Urine flow and sodium excretion were markedly increased by potassium infusion. Systemic blood pressure was not influenced by ANG II injection because of administration of a small dose into the renal artery. Renal vascular response to ANG II was attenuated when plasma K⁺ concentration was increased by acute potassium infusion. As seen in Fig. 1-A, percent changes in RBF produced by ANG II injection were −35.8 ± 9.8% in the control period, −26.1 ± 8.4% in the potassium period and −30.4 ± 7.8% in the recovery period. Percent RBF reduction produced by ANG II injection in the potassium period was significantly less than those obtained in the control and recovery periods (p < 0.05).

**Experiment II:**

As shown in Table II, plasma K⁺ concentration was 3.47 ± 0.25 mEq/L in the control period, 5.45 ± 0.25 mEq/L in the potassium period and 4.55 ± 0.21 mEq/L in the recovery period. MAP and plasma sodium concentration did not differ in the three periods. RBF also was not significantly changed by potassium infusion. Urine flow and sodium excretion was increased by potassium infusion and decreased after cessation of potassium infusion. These changes were similar to the results of experiment I. Percent changes in RBF produced by PGE₂ were +44.2 ± 10.5% in the control period, +50.5 ± 6.8% in the potassium period and +44.9 ± 7.2% in the recovery period, as seen in Fig. 1-B. These percent change values among the three periods were not significant. However, the absolute RBF increase (+3.9 ± 1.1 ml/min/kg) produced by PGE₂ injection in the potassium period was significantly greater than that (+3.1 ± 1.0 ml/min/kg) obtained in the control period (p < 0.01). This result indicates that contrary to the results of vascular response to ANG II, renal vascular response to PGE₂ showed a tendency to be potentiated when plasma K⁺ concentration was increased.

**DISCUSSION**

Intravenous infusion of potassium in normal dogs markedly increased urine flow and sodium excretion with an elevation of plasma K⁺ concentration in both experiments I and II, but the systemic blood pressure and plasma sodium concentration were not significantly changed. These results are consistent with previous reports. In the control period, mean RBF/kg body weight was greater in experiment I than in experiment II and mean urinary sodium excretion was less in experiment I than in experiment II. These differences may be due in part to differences in the body weights of the dogs in the two groups. An elevation of plasma K⁺ concentration by potassium infusion also had an effect on renal vascular reactivity, i.e. it attenuated the renal vascular response to ANG II. On the other hand, renal vascular response to PGE₂ was not attenuated but rather tended to be potentiated by elevation of plasma K⁺ concentration.

Hollenberg et al. have found that a high potassium intake in normal man enhanced the renal vascular response to ANG II and the mechanism was suggested as being due to a decrease in occupied ANG II receptors following suppression of endogenous angiotensin II by a high potassium intake. However, potassium infusion reduced the vascular response to ANG II and PRA showed a tendency to be suppressed by potassium infusion in the present study. Therefore, our result is not explained by the occupied ANG II receptor theory. Besides, in the results of Hollenberg et al., the plasma K⁺ concentration was not changed by a high potassium diet. Since in our study the plasma K⁺ concentration was increased by potassium infusion, reduced ANG II responsiveness observed during potassium infusion may be due to changes in plasma K⁺ concentration itself. Frohlich et al. have reported that in the dog kidney and forelimb, the vascular response to norepinephrine was decreased by KCl infusion into the renal or brachial artery. Kondo et al. have found that a slight increase in potassium concentration in the perfusate reduced the vascular response to norepinephrine in rat mesenteric artery and this effect of potassium on vascular reactivity was inhibited in the presence of ouabain. Therefore, they postulated stimulation of Na-K ATPase activity produced by an elevation of perfusate K⁺ concentration as a possible mechanism of the reduced NE response. It is known that local elevation of the extracellular potassium within the physiological range causes arterial dilatation through stimulation of Na-K ATPase activity in the vascular membrane. In our experiment, RBF showed a tendency to increase with an elevation of plasma K⁺ concentration. The reduced ANG II responsiveness observed when plasma K⁺ concentration was

*Japanese Circulation Journal Vol. 50, March 1986*
increased may also be due to the change in Na-K ATPase activity.

On the other hand, percent increase in RBF induced by the depressor agent PGE₂ did not change significantly with elevation of plasma K⁺ concentration. However, the absolute increase in RBF induced by PGE₂ in the potassium period was greater than that in the control period. As seen in Table II, RBF was increased from 6.7 ± 1.1 to 7.7 ± 2.0 ml/min/kg in the potassium period, though the increase was not significant. This high RBF value in the potassium period may be the reason why the percent change in RBF induced by PGE₂ in the potassium period did not show a significant difference compared with that in the control period. The mechanism by which an elevation of plasma K⁺ concentration potentiated the dilatation of renal vessels by PGE₂ is quite unclear. The changes in the vascular response to ANG II and PGE₂ observed by elevation of plasma K⁺ concentration in our study seem to act towards lowering the blood pressure.

REFERENCE